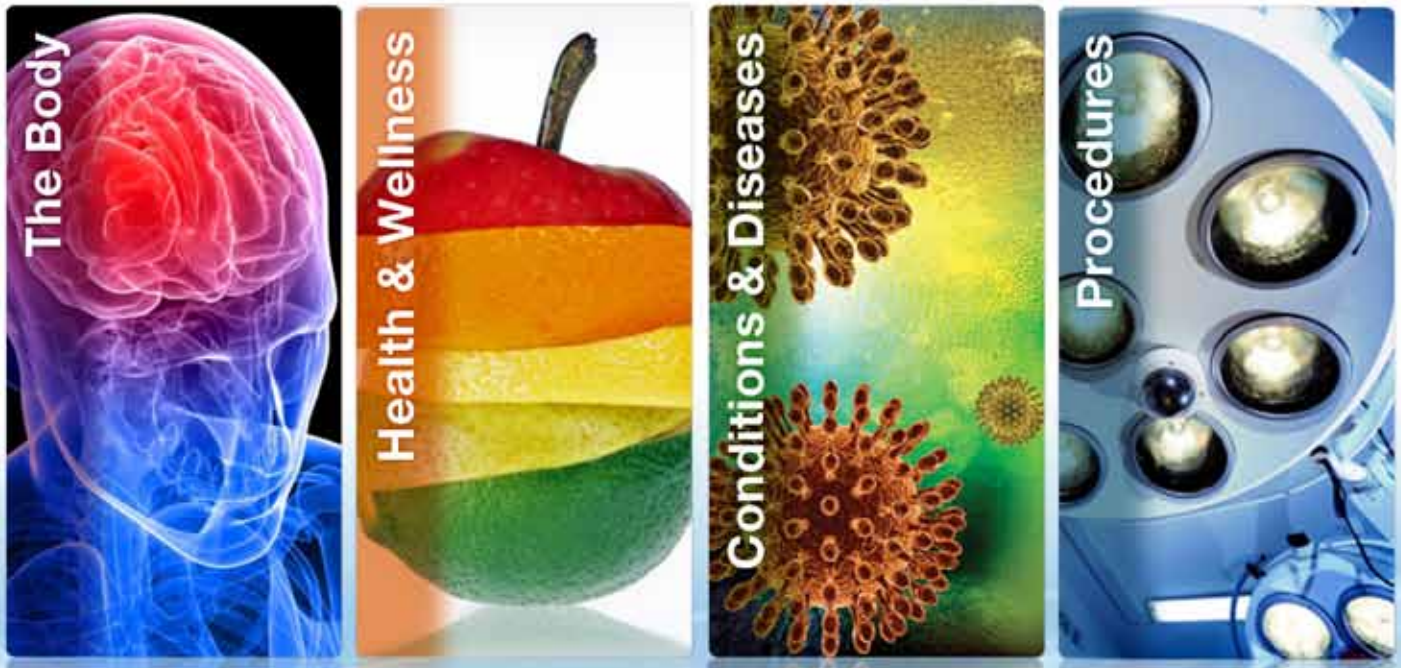
MAY 2013

accomplishments



Intramural Research Program

Our Research Changes Lives

one program
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infinite possibilities

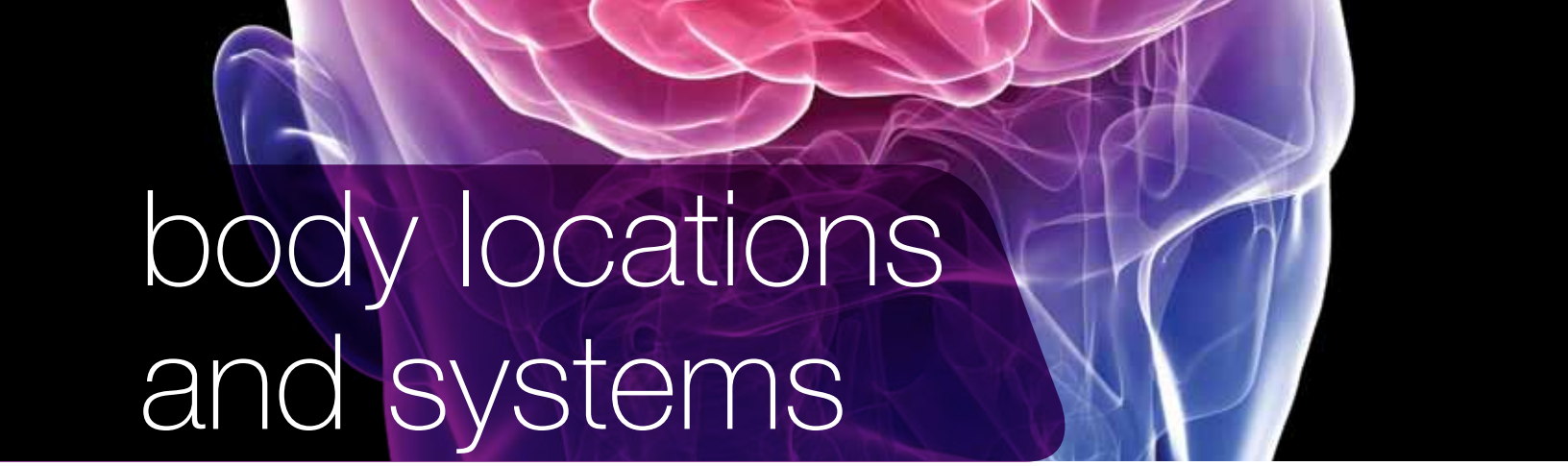
irp.nih.gov

accomplishments

IRP researchers have won international recognition and countless awards for research that is truly game-changing—transformational science that advances biomedical knowledge.

The following is a snapshot of some of the IRP's most outstanding research.

Contents



body locations and systems

Endocrine System (Hormones)

2012: Taking a closer look at our on/off relationship with insulin

Challenge

Diabetes now affects more than 25 million people of all ages[1] yet the molecular underpinnings of the disease remain unclear. Although the overall pathways that drive the production of insulin are known, the molecular mechanisms that control rapid changes in insulin synthesis—for example following a meal—are not.

Advance

IRP investigators led by Eun Kyung Lee, Ph.D., identified a previously unknown component of the pathway—an RNA-binding protein named HuD, expressed in pancreatic β cells—that can bind insulin mRNA and inhibit its translation into protein, essentially blocking its production. The researchers also showed that, in response to increased glucose levels, HuD releases insulin mRNA, allowing the production of insulin protein.

Impact

The discovery that an RNA-binding protein can repress insulin translation in a rapidly reversible manner suggests that deficiencies in this protein could underlie some cases of diabetes. Work is underway to systematically compare HuD in the pancreatic β cells of diabetic and non-diabetic subjects, with the aim of determining if HuD could be a new therapeutic target.

Publications

Lee EK, Kim W, Tominaga K, Martindale JL, Yang X, Subaran SS, Carlson OD, Mercken EM, Kulkarni RN, Akamatsu W, Okano H, Perrone-Bizzozero NI, de Cabo R, Egan JM, Gorospe M. RNA-binding protein HuD controls insulin translation. *Mol Cell*. 2012 Mar 30;45(6):826-35.

2011: Tracking the devastating effects of diethylstilbestrol (DES), a trans-placental carcinogen

Challenge

Between 1940 and the early 1970s, millions of pregnant women were given diethylstilbestrol (DES), the first synthetic estrogen, to prevent pregnancy complications. DES was later found to be a carcinogen that could cross the placenta and cause a range of health-related issues in women, including developmental defects and cancers. Rigorous follow-up reporting and analysis would be required to fully understand the devastating effects of DES on the women who were exposed in utero years before.

1 http://diabetes.niddk.nih.gov/dm/pubs/statistics/#fast

Advance

IRP investigators led by Robert Hoover, M.D., Sc.D., re-contacted more than 4,600 women who had participated in an initial landmark study, which described a rare vaginal cancer typically seen only in older women. These women were then followed long-term, and researchers were able to identify and track a number of adverse health outcomes linked to DES exposure, including pre-term delivery, ectopic pregnancy, and cancers of the cervix.

Impact

Without long-term follow-up studies, many outcomes of DES exposure might have gone unreported. This investigation, and others like it, serves as a model for an entire area of research focused on the role of endocrine disruption in early life and subsequent health effects.

Publications

Hoover RN, Hyer M, Pfeiffer RM, Adam E, Bond B, Cheville AL, Colton T, Hartge P, Hatch EE, Herbst AL, Karlan BY, Kaufman R, Noller KL, Palmer JR, Robboy SJ, Saal RC, Strohsnitter W, Titus-Ernstoff L, Troisi R. Adverse health outcomes in women exposed in utero to diethylstilbestrol. *N Engl J Med.* 2011 6;365(14):1304-14.

Immune System

2012: Discovering monogenic forms of common variable immunogenicity

Challenge

Common variable immunodeficiency (CVID) is one of the most common primary immunodeficiency diagnoses[2], but can take three to five years to be reached due to the non-specific nature of the symptoms. Early diagnosis of CVID is essential to ensuring reduced severity of infections via intravenous immunoglobulin (IVIG) treatment.

Advance

IRP researchers E. Michael Gertz, Ph.D., Alejandro A. Schäffer, Ph.D., and colleagues used genetic linkage analysis in families to identify homozygous mutations in the lipopolysaccharide responsive beige-like anchor gene (*LRBA*) as a frequent cause of CVID in patients who have early onset and autoimmune manifestations.

Impact

LRBA-deficient patients can now receive a prompt diagnosis via genetic analysis and start IVIG treatment sooner, which helps reduce the severity of recurrent infections and improves overall outcomes.

Publications

Lopez-Herrera G, Tampella G, Pan-Hammarström Q, Herholz P, Trujillo-Vargas CM, Phadwal K, Simon AK, Moutschen M, Etzioni A, Mory A, Srugo I, Melamed D, Hultenby K, Liu C, Baronio M, Vitali M, Philippet P, Dideberg V, Aghamohammadi A, Rezaei N, Enright V, Du L, Salzer U, Eibel H, Pfeifer D, Veelken H, Stauss H, Lougaris V, Plebani A, Gertz EM, Schäffer AA, Hammarström L, Grimbacher B. Deleterious Mutations in LRBA Are Associated with a Syndrome of Immune Deficiency and Autoimmunity. *Am J Hum Genet.* 2012 8;90(6):986–1001.

2 http://www.aaaai.org/conditions-and-treatments/primary-immunodeficiency-disease/common-variable-immunodeficiency.aspx

2011: Reclassification of diseases improves understanding and outcomes

Challenge

Little is known about the causes or how to treat a group of rare heterogeneous autoimmune muscle diseases called idiopathic inflammatory myopathies, including Dermatomyositis, Polymyositis, and Inclusion Body Myositis. For unknown reasons, these diseases are increasing in prevalence in both children and adults, and a better understanding of their pathogenesis, underlying genetics, and molecular basis is urgently needed.

Advance

IRP researchers led by Frederick W. Miller, M.D., Ph.D., took a novel approach to understanding these heterogeneous syndromes and showed that the genetic and environmental risk factors, symptoms, and responses to therapy and prognosis can be predicted by categorizing the syndromes into mutually exclusive and stable phenotypes based on clinical and immune response features.

Impact

Redefining autoimmune muscle diseases into novel phenotypes has advanced the understanding of their unique pathogenesis and helped clinicians to recognize and manage these debilitating disorders.

Publications

Rider LG, Miller FW. Deciphering the clinical presentations, pathogenesis, and treatment of the idiopathic inflammatory myopathies. *JAMA*. 2011 Jan 12;305(2):183-90. doi: 10.1001/jama.2010.1977.

Miller FW. New approaches to the assessment and treatment of the idiopathic inflammatory myopathies. *Ann Rheum Dis*. 2012 Apr;71 Suppl 2:i82-5.

Mental Health and Behavior

2012: Spur of the moment purchase? Blame your orbitofrontal cortex

Challenge

Scientists have long assumed that an area of the brain called the orbitofrontal cortex plays a role in decision-making. While the idea gained widespread acceptance in the scientific community, it was based on correlative evidence. New research was needed to determine exactly what role the region plays, and how that may affect our understanding of certain diseases, for example addiction disorders.

Advance

IRP researchers led by Geoffrey Schoenbaum, M.D., Ph.D., designed a series of experiments and discovered that the orbitofrontal cortex in fact does play a role in decision-making, but only in spur-of-the-moment, quick decisions and not decisions made previously or through habit. This finding was true for both decision-making and learning—in other words, if a decision is assumed and doesn't occur, that knowledge can be used to drive the process of learning.

Impact

This research fundamentally changed scientific understanding of the orbitofrontal cortex's role in normal behavior and how its alteration may contribute to behaviors seen in addiction disorders. Future work will characterize how drugs such as cocaine adversely affect this region of the brain, as well as identify pre-clinical approaches to restore function to damaged regions.

Publications

Jones JL, Esber GR, McDannald MA, Gruber AJ, Hernandez A, Mirenzi A, Schoenbaum G. Orbitofrontal cortex supports behavior and learning using inferred but not cached values. *Science*. 2012 Nov 16;338(6109):953-6.

2011: Stimulating new ideas on caffeine action in the brain

Challenge

Caffeine is one of the oldest and most widely consumed cognitive stimulants on earth. Although it has pharmacological effects on many brain areas, its primary physiological site of action has not been established. Understanding how caffeine functions may provide clues to understanding sleep disorders, depression, and a range of conditions involving altered cognitive functioning.

Advance

IRP researchers led by Serena Dudek, Ph.D., discovered that caffeine, at levels similar to that consumed by humans, along with similar, more selective A1 adenosine receptor blockers, strongly enhanced synaptic responses in an area of the brain known as "hippocampal area CA2." The hippocampus is known for its role in learning and memory.

Impact

By discovering that this small region of the brain is the primary site of caffeine action, these studies highlight the CA2 region as a potential target for drug development to combat symptoms of fatigue due to sleep deprivation and depression, as well as sleep disturbances in neurodevelopmental disorders such as autism.

Publications

Simons SB, Caruana DA, Zhao M, Dudek SM. Caffeine-induced synaptic potentiation in hippocampal CA2 neurons. *Nat Neurosci*. 2011 Nov 20;15(1):23-5.

2010: The need for speed: A new approach to treating depressive disorders

Challenge

Current therapies for depressive disorders take many weeks to work, during which time the symptoms of depression, including suicidal thinking, persist and can be fatal. Patients need better treatments that begin relieving symptoms immediately.

Advance

IRP researchers led by Carlos A. Zarate, M.D., took a novel approach to the problem and discovered that a single infusion of ketamine provides a fast, robust, and sustained antidepressant effect, including reduction of suicidal thoughts within minutes.

Impact

Having demonstrated unprecedented speed of symptom relief, ketamine and its analogs are now being tested in clinical trials around the world and, if approved for use, could become a new standard of care for treating people with depressive disorders.

Publications

DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, Machado-Vieira R, Zarate CA Jr. Rapid resolution of suicidal ideation after a single ketamine infusion in patients with treatment-resistant major depression. *J Clin Psychiatry*. 2010;71:1605-11.

2008: Could you become addicted to something? Your genes reveal all

Challenge

Genetic influences on quitting smoking and beginning use of common addictive substances are well documented in the scientific literature. Doctors recommend prevention interventions for individuals who may be at risk of substance abuse. However, a test is needed to indicate the most urgent candidates for prevention intervention.

Advance

IRP researchers at the National Institute on Drug Abuse (NIDA) developed the first genetic test for smoking cessation and discovered that the test's score is able to robustly separate individuals who rapidly accelerate use of addictive substances from those who do not.

Impact

This is the first test to identify individuals at risk for addiction, who might benefit most from prevention efforts since they are more likely to escalate use if they start and have more difficulty quitting if they develop regular use, abuse, and dependence.

Publications

Uhl GR, Liu QR, Drgon T, Johnson C, Walther D, Rose JE, David SP, Niaura R, Lerman C. Molecular genetics of successful smoking cessation: convergent genome-wide association study results. *Arch Gen Psychiatry.* 2008 Jun;65(6):683-93.

Drgon T, Montoya I, Johnson C, Liu QR, Walther D, Hamer D, Uhl GR. Genome-wide association for nicotine dependence and smoking cessation success in NIH research volunteers. *Mol Med*. 2009 Jan-Feb;15(1-2):21-7.

1970: A sense of calm in bipolar disorder: The clinical trials of lithium

Challenge

In 1949, the Australian physician John Cade published a paper on using lithium salts to treat psychotic mania, noting that the drug produced a "pronounced calming effect"[3]. The publication piqued great interest among the psychiatry community, but large multicenter clinical studies were needed to confirm lithium's role as a potential new tool in the treatment of mania associated with bipolar disorder.

3 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2560740/pdf/10885180.pdf

Advance

In the decades following Cade's publication, the National Institute of Mental Health (NIMH) and several university centers established large, rigorously controlled, multicenter clinical trials that clearly demonstrated the antimanic effects of lithium. The ability to convene, lead, and analyze data from these trials contributed to the FDA's 1970 approval of lithium to treat acute mania.

Impact

More than 60 years after its discovery, lithium is still the first-line therapy for treatment of bipolar disorder. In addition to being tremendously successful in treating the illness, lithium provides enormous financial savings by reducing the lost productivity of affected earners, homemakers, caregivers, and other individuals by billions of dollars annually[4].

Publications

1970 Eskalith Approval: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.

4 http://www.ncbi.nlm.nih.gov/pubmed/11433880

health & wellness

Environmental Health

1992/2012: Linking heavy exposure to diesel exhaust to lung cancer deaths in miners

Challenge

Despite numerous studies investigating the relationship between diesel engine exhaust exposure and risk of death from lung cancer, the lack of quantitative exposure data and large sample sizes restricted our ability to accurately evaluate this risk. Accurate evaluation of the exposure-response for diesel exhaust and lung cancer is critical for the millions of people around the world who are occupationally exposed to potentially fatal carcinogens.

Advance

In 1992, IRP researchers led by Debra T. Silverman, Sc.D., and colleagues at the National Institute for Occupational Safety and Health (NIOSH) embarked on a 20-year study of more than 12,000 miners, which became the first to show a statistically significant association between heavy exposure to diesel exhaust and lung cancer death.

Impact

These findings are important for public health, with implications for not only the 1.4 million American workers who are exposed to diesel exhaust in the workplace[5], but also the many millions of urban populations in the U.S. and around the world who may be exposed to diesel exhaust.

Publications

Silverman DT, Samanic CM, Lubin JH, Blair AE, Stewart PA, Vermeulen R, Coble JB, Rothman N, Schleiff PL, Travis WD, Ziegler RG, Wacholder S, Attfield MD. The Diesel Exhaust in Miners study: a nested case-control study of lung cancer and diesel exhaust. *J Natl Cancer Inst.* 2012 6;104(11):855-68.

1957: Fluoridation: A public health milestone to make us all smile

Challenge

More than half a century ago, tooth loss and decay was a serious public health issue afflicting most people, often at a young age. Periodontal diseases and dental caries left 17 million Americans age 45 and older (about three in 10) with none of their natural teeth[6]. If researchers could discover a way to prevent tooth decay, everyone would benefit.

5 http://monographs.iarc.fr/ENG/Publications/techrep42/TR42-Full.pdf
6 http://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=129

Advance

IRP investigators at the National Institute of Dental Research (now the National Institute of Dental and Craniofacial Research (NIDCR)) spearheaded studies in the 1940s and 1950s that showed the rate of tooth decay in children who drank fluoridated water fell more than 60 percent.

Impact

Water fluoridation stands out as one of the most significant and cost-effective public health milestones of the last century.

Publications

Francis A. Arnold, Jr. Grand Rapids Fluoridation Study—Results Pertaining to the Eleventh Year of Fluoridation. *Am J Public Health Nations Health*. 1957 May;47(5):539–545.

The Story of Fluoridation - http://www.nidcr.nih.gov/oralhealth/topics/fluoride/thestoryoffluoridation.htm.

Substance Abuse

2012: A non-addictive form of cocaine? A potential therapy awaits

Challenge

Cocaine addiction is a chronic and relapsing disorder that affects millions worldwide[7], exerting a toll in lives lost, families torn, and communities destroyed. No medications are currently available to treat cocaine addiction.

Advance

IRP and international researchers led by Amy Hauck Newman, Ph.D., discovered that R-modafinil, like cocaine, inhibits dopamine uptake, but binds to the dopamine transporter in a unique fashion that may not result in the same addictive response as cocaine.

Impact

Molecular and preclinical pharmacological findings support translation of R-modafinil studies to clinical trials in the cocaine-abusing population as a potential treatment.

Publications

Loland CJ, Mereu M, Okunola OM, Cao J, Prisinzano TE, Mazier S, Kopajtic T, Shi L, Katz JL, Tanda G, Newman AH. R-modafinil (armodafinil): a unique dopamine uptake inhibitor and potential medication for psychostimulant abuse. *Biol Psychiatry*. 2012 Sep 1;72(5):405-13.

2012: Chronic drinking may alter the brain and increase PTSD risk

Challenge

While alcoholism and anxiety disorders like post-traumatic stress disorder (PTSD) are often seen together, few studies have explored how chronic alcohol exposure can affect recovery from a traumatic experience.

7 http://www.thelancet.com/series/addiction

Advance

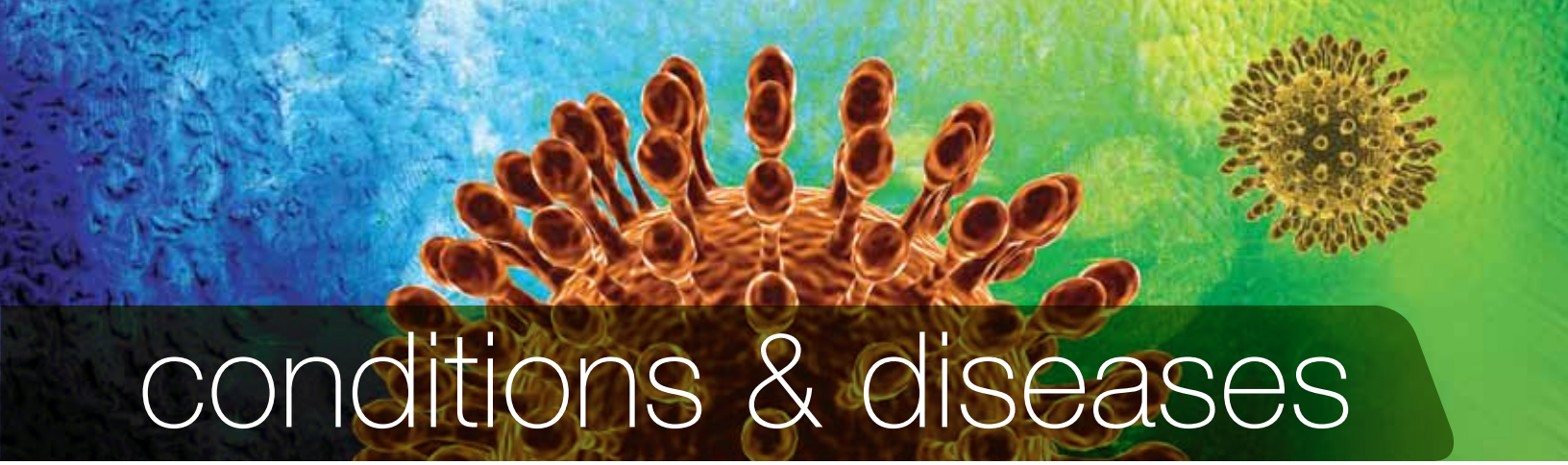
Andrew Holmes, Ph.D., and colleagues used an animal model to determine that chronic alcohol exposure remodels the brain's neuronal wiring, impairing the ability to suppress fear and recover normally from a traumatic experience.

Impact

The results show that chronic drinking rewires brain circuitry, which may increase susceptibility for anxiety disorders like PTSD. These findings provide a basis for the development of neurochemical therapies that target these specific areas of the brain with an aim to restoring normal functions.

Publications

Holmes A, Fitzgerald PJ, MacPherson KP, DeBrouse L, Colacicco G, Flynn SM, Masneuf S, Pleil KE, Li C, Marcinkiewcz CA, Kash TL, Gunduz-Cinar O, Camp M. Chronic alcohol remodels prefrontal neurons and disrupts NMDAR-mediated fear extinction encoding. *Nat Neurosci*. 2012 Oct;15(10):1359-61.



conditions & diseases

Cancers

2001(+): The HPV vaccine: Two decades of research pays off

Challenge

Human papillomavirus (HPV) is the most common sexually-transmitted infection around the world[8]. With more than 40 variations and clear linkages to cervical cancer and a range of genital cancers[9], the challenge to develop a broadly protective vaccine was unparalleled.

Advance

Douglas R. Lowy, M.D., and John T. Schiller, Ph.D., spent more than two decades investigating how to prevent HPV infection, culminating in the discovery and production of virus-like particles (VLPs), which block certain mechanisms essential to HPV infection. Their work led to the production of the first commercially available vaccine against the two deadliest forms of the virus, HPV16 and HPV18, in 2006.

Impact

The HPV vaccine has been shown to be 100 percent effective, and governments across the globe now recommend routine vaccination of all girls (and in some countries, boys) aged 11 or 12 years. The hope is that widespread vaccination could reduce HPV-associated cancer deaths by up to two-thirds[10].

Publications

Harro CD, Pang YY, Roden RB, Hildesheim A, Wang Z, Reynolds MJ, Mast TC, Robinson R, Murphy BR, Karron RA, Dillner J, Schiller JT, Lowy DR. Safety and immunogenicity trial in adult volunteers of a human papillomavirus 16 L1 virus-like particle vaccine. *J Natl Cancer Inst*. 2001;93:284-292.

FDA Licenses New Vaccine for Prevention of Cervical Cancer and Other Diseases in Females Caused by Human Papillomavirus *Rapid Approval Marks Major Advancement in Public Health:* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108666.htm.

8 http://www.cdc.gov/std/hpv/stdfact-hpv.htm
9 http://www.cdc.gov/cancer/hpv/
10 http://www.cancer.gov/cancertopics/factsheet/prevention/HPV-vaccine

2000(+): Finding one disease is actually many: Diffuse large B-cell lymphomas

Challenge

Some patients with diffuse large B-cell lymphomas (DLBCL) live longer and respond better to therapy than others, highlighting an urgent need to better understand the disease's underlying biology and inform more effective treatment approaches.

Advance

IRP researchers led by Louis Staudt, M.D., Ph.D., profiled the genes expressed in patients with DLBCL and found important differences, leading to the identification of three new molecularly and clinically distinct subclasses of the disease: germinal center B-cell-like, activated B-cell-like (ABC), and primary mediastinal B-cell lymphoma (PMBL).

Impact

These discoveries revealed new molecular targets based on each subclass and informed the development of new therapies. For example, the discovery that one subgroup of DLBCL relies on the NF-kB signaling pathway allowed physicians to target that pathway directly, leading to complete remission in a number of cases.

Publications

Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, Boldrick JC, Sabet H, Tran T, Yu X, Powell JI, Yang L, Marti GE, Moore T, Hudson J Jr, Lu L, Lewis DB, Tibshirani R, Sherlock G, Chan WC, Greiner TC, Weisenburger DD, Armitage JO, Warnke R, Levy R, Wilson W, Grever MR, Byrd JC, Botstein D, Brown PO, Staudt LM. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*. 2000 Feb 3;403(6769)

Wright G, Tan B, Rosenwald A, Hurt EH, Wiestner A, Staudt LM. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. *Proc Natl Acad Sci U S A*. 2003 Aug 19;100(17):9991-6.

1995: Lifting the lid on kidney cancer: Exposing the underlying genetics

Challenge

In the early 1980s, little was known about the genetic basis of kidney cancer, and patients continued to succumb to the disease despite chemotherapy treatment. Today, more than 13,000 renal carcinoma patients in the U.S. still die every year[11], demonstrating a continuing need for better approaches to battling this disease

Advance

During the past two decades, W. Marston Linehan, M.D., and colleagues made seminal discoveries about the genetic basis of kidney cancer, including identification of the von Hippel-Lindau (VHL) gene (the 6th human cancer gene identified) and the hereditary papillary renal cell carcinoma (HPRC), hereditary leiomyomatosis, and renal cell cancer (HLRCC) genes: *c-Met*, *BHD*, and *fumarate hydratase*.

Impact

These discoveries have led to new approaches for molecular-based therapies against renal carcinoma, and clinical trials are now ongoing with a number of promising treatments.

11 http://www.cancer.gov/cancertopics/types/kidney

Publications

Linehan WM, Lerman MI, Zbar B. Identification of the von Hippel-Lindau (VHL) gene. Its role in renal cancer. *JAMA*. 1995 Feb 15;273(7):564-70.

Schmidt L, Duh FM, Chen F, Kishida T, Glenn G, Choyke P, Scherer SW, Zhuang Z, Lubensky I, Dean M, Allikmets R, Chidambaram A, Bergerheim UR, Feltis JT, Casadevall C, Zamarron A, Bernues M, Richard S, Lips CJ, Walther MM, Tsui LC, Geil L, Orcutt ML, Stackhouse T, Lipan J, Slife L, Brauch H, Decker J, Niehans G, Hughson MD, Moch H, Storkel S, Lerman MI, Linehan WM, Zbar B. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. *Nat Genet*. 1997 May;16(1):68-73.

Toro JR, Nickerson ML, Wei MH, Warren MB, Glenn GM, Turner ML, Stewart L, Duray P, Tourre O, Sharma N, Choyke P, Stratton P, Merino M, Walther MM, Linehan WM, Schmidt LS, Zbar B. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. *Am J Hum Genet*. 2003 Jul;73(1):95-106.

1989(+): Discovering a growth factor and its incredible healing powers

Challenge

For decades, nothing was available to prevent or reduce the severity of oral mucositis (ulcerative lesions of the mouth), a common side effect of high doses of chemotherapy and radiation, which increases the risk of infection in cancer patients. A therapy was needed to reduce the incidence of this painful and life-threatening side-effect of many cancer therapies.

Advance

In the late 1980s, IRP scientists Jeffrey Rubin, M.D., Ph.D., Paul Finch, Ph.D., and Stuart A. Aaronson, M.D., discovered and purified keratinocyte growth factor (KGF). Several studies later demonstrated that KGF occurs naturally and stimulates the growth of surface layer cells in the mouth, which speeds healing of ulcers, reducing infection risks. The NIH partnered with Amgen in 1992 to develop Kepivance, a therapeutic treatment based on KGF.

Impact

Clinical trial results showed that Kepivance decreased the incidence and duration of severe oral mucositis in cancer patients who were given intensive chemotherapy and radiation prior to bone marrow/blood cell transplants. FDA approved in 2004, Kepivance now benefits about 11,000 American adults who undergo bone marrow transplants each year[12].

Publications

Rubin JS, Osada H, Finch PW, Taylor WG, Rudikoff S, Aaronson SA. Purification and characterization of a newly identified growth factor specific for epithelial cells. *Proc Natl Acad Sci U S A*. 1989 Feb;86(3):802-6.

Kepivance FDA Approval Package: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/125103s000_KepivanceTOC.cfm

12 http://www.amgen.com/media/media_pr_detail.jsp?year=&releaseID=655220

Genetics and Birth Defects

2012: DNA and damage control: A complex web of players

Challenge

Fanconi anemia (FA) is a genetic disease characterized by congenital defects, bone marrow failure, and cancer susceptibility. At least 15 genes are known to be involved in the disease[13], whose gene products normally constitute a DNA damage response network that is essential for repair of DNA strand damage. Understanding how FA proteins are recruited to the DNA damage sites could uncover new drug targets.

Advance

IRP investigators led by Zhijiang Yan, Ph.D., showed for the first time that the FA network is controlled by a novel ubiquitin signaling cascade initiated by the RNF8 ubiquitin ligase and its partner, UBC13, and mediated by FAAP20, a newly described component of the FA core complex.

Impact

Transmission of DNA damage signals is vital in setting the rate and extent of DNA repair during aging and the development of cancer. The newly discovered cascade is now a potential target for drug intervention: agonists that promote repair could aid in the function of aging cells, whereas antagonists that inhibit the cascade could disrupt DNA repair in cancer cells to make them more susceptible to chemotherapy.

Publications

Yan Z, Guo R, Paramasivam M, Shen W, Ling C, Fox D 3rd, Wang Y, Oostra AB, Kuehl J, Lee DY, Takata M, Hoatlin ME, Schindler D, Joenje H, de Winter JP, Li L, Seidman MM, Wang W. A ubiquitin-binding protein, FAAP20, links RNF8-mediated ubiquitination to the Fanconi anemia DNA repair network. *Mol Cell*. 2012 Jul 13;47(1):61-75.

2011: Team science unravels the link between ALS and FTD

Challenge

Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) is a fatal neurodegenerative disorder that leads to progressive paralysis and respiratory failure[14]. Frontotemporal dementia (FTD) is the most common form of dementia in the under-65 population[15]. Researchers have long suspected an overlap between the two diseases, but the molecular and genetic basis of this intersection was unknown.

Advance

Bryan J. Traynor, M.D., Ph.D., brought historically competitive research groups together to focus their efforts on identifying the underlying genetic cause of ALS and FTD. The new international consortium discovered that an insertion mutation disrupting the *C9ORF72* gene is the most common genetic cause of both ALS and FTD identified to date, accounting for 40 percent of all familial cases of ALS and FTD in European and North American populations.

Impact

Discovery of this mutation changed scientific understanding of neurodegenerative diseases, influencing the diagnosis and investigation of ALS and FTD and, for the first time, mechanistically linking the two disorders. It also suggested a therapeutic target for gene therapy, with further research ongoing.

13 http://ghr.nlm.nih.gov/condition/fanconi-anemia
14 http://www.ninds.nih.gov/disorders/amyotrophiclateralsclerosis/detail_ALS.htm
15 http://www.aafp.org/afp/2010/1201/p1372.html

Publications

Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, Schymick JC, Laaksovirta H, van Swieten JC, Myllykangas L, Kalimo H, Paetau A, Abramzon Y, Remes AM, Kaganovich A, Scholz SW, Duckworth J, Ding J, Harmer DW, Hernandez DG, Johnson JO, Mok K, Ryten M, Trabzuni D, Guerreiro RJ, Orrell RW, Neal J, Murray A, Pearson J, Jansen IE, Sondervan D, Seelaar H, Blake D, Young K, Halliwell N, Callister JB, Toulson G, Richardson A, Gerhard A, Snowden J, Mann D, Neary D, Nalls MA, Peuralinna T, Jansson L, Isoviita VM, Kaivorinne AL, Hölttä-Vuori M, Ikonen E, Sulkava R, Benatar M, Wuu J, Chiò A, Restagno G, Borghero G, Sabatelli M; ITALSGEN Consortium, Heckerman D, Rogaeva E, Zinman L, Rothstein JD, Sendtner M, Drepper C, Eichler EE, Alkan C, Abdullaev Z, Pack SD, Dutra A, Pak E, Hardy J, Singleton A, Williams NM, Heutink P, Pickering-Brown S, Morris HR, Tienari PJ, Traynor BJ. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron*. 2011 Oct 20;72(2):257-68.

1997(+): Breaking down complex autoinflammatory diseases, and building up new hope

Challenge

In some individuals, the immune system attacks the body's own tissues, causing inflammation. The recent discovery that a subset of autoinflammatory diseases has genetic components complicates diagnosis, making development of therapeutics a challenge.

Advance

Daniel L. Kastner, M.D., Ph.D., and colleagues have identified, classified, and characterized more than 10 new hereditary autoinflammatory disease pathways, including FMF, TRAPS, NOMID, and DIRA. IRP scientists develop and test new therapies aimed at reducing inflammation in these diseases, in some cases completely reversing them.

Impact

Patients with complex genetic autoinflammatory disorders may soon no longer need to experience trial and error prescribing in an effort to control their debilitating symptoms. For some diseases, genetic analyses combined with molecular studies of the affected pathways can inform the selection of targeted therapeutics and provide immediate and sustained relief.

Publications

International FMF Consortium (Kastner DL, corresponding author). Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell*. 1997;90:797-807.

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Aksentijevich I, Nowak M, Mallah M, Chae JJ, Watford WT, Hofmann SR, Stein L, Russo R, Goldsmith D, Dent P, Rosenberg HF, Austin F, Remmers EF, Balow JE Jr, Rosenzweig S, Komarow H, Shoham NG, Wood G, Jones J, Mangra N, Carrero H, Adams BS, Moore TL, Schikler K, Hoffman H, Lovell DJ, Lipnick R, Barron K, O'Shea JJ, Kastner DL, Goldbach-Mansky R. De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. *Arthritis Rheum*. 2002;46:3340-3348.

Infections

2001(+): Identifying and understanding rare immune system diseases

Challenge

Primary immune deficiency diseases (PIDDs) are rare difficult-to-manage disorders caused by inherited defects in cells of the immune system[16]. They can result in increased risk of life-threatening infections, autoimmune diseases, and tumors[17]. Understanding the molecular mechanisms underlying these immunodeficiencies is crucial to therapeutic decision-making and effective management of each disease.

Advance

For more than 30 years, IRP investigators at the National Institute of Allergy and Infectious Diseases (NIAID) have studied and developed new treatments for known PIDDs and worked to decipher immunodeficiencies of unknown etiology. In the last few years alone, IRP scientists identified:

- NEMO immunodeficiency, which leads to frequent bacterial and viral infections and abnormal teeth, hair, skin, and nails
- DOCK8 immunodeficiency, which can cause persistent skin infections, allergies, and cancer
- XMEN disease, characterized by persistent Epstein-Barr virus infections and magnesium deficiency
- PLAID, characterized by immune deficiency, autoimmunity, inflammatory skin disorders, and cold-induced hives

Impact

IRP researchers and their collaborators have made significant contributions to current understanding of PIDDs and to the treatment of patients affected by these devastating diseases. In 2007, NIAID opened a Primary Immune Deficiency Clinic at the NIH Clinical Center to provide a focus of IRP expertise for referring physicians and their patients. The clinic accepts patients with known or suspected PIDDs and offers treatment recommendations and, in some cases, a disease diagnosis.

Publications

Press Release – NIAID Initiative Addresses Primary Immune Deficiency Diseases: http://www.niaid.nih.gov/news/newsreleases/2003/Pages/pirc.aspx.

Jain A, Ma CA, Liu S, Brown M, Cohen J, Strober W. Specific missense mutations in NEMO result in hyper-IgM syndrome with hypohydrotic ectodermal dysplasia. *Nat Immunol*. 2001 Mar;2(3):223-8.

Zhang Q, Davis JC, Lamborn IT, Freeman AF, Jing H, Favreau AJ, Matthews HF, Davis J, Turner ML, Uzel G, Holland SM, Su HC. Combined immunodeficiency associated with DOCK8 mutations. *N Engl J Med*. 2009 Nov 19;361(21):2046-55.

1989: Protecting at-risk children from a severe respiratory disease

Challenge

Respiratory syncytial virus (RSV) is a leading cause of bronchiolitis and pneumonia in children less than one year old[18]. RSV infection can be life-threatening, especially for babies born prematurely or with health problems such as chronic lung disease or congenital heart disease[19]. An effective means to prevent severe RSV disease was needed.

16 http://www.niaid.nih.gov/topics/immuneDeficiency/Understanding/Pages/quickFacts.aspx
17 http://www.niaid.nih.gov/about/yearinreview/advances/scientificFindings/Pages/AddressingImmuneMediatedDiseases.aspx
18 http://www.cdc.gov/rsv/about/faq.html
19 http://www.cdc.gov/rsv/about/faq.html

Advance

IRP investigators Robert M. Chanock, M.D., Brian Murphy, M.D., and colleagues showed that giving anti-RSV antibodies to animals protected them from RSV infection. The researchers then developed a monoclonal antibody that neutralized RSV in animal models. The pharmaceutical company MedImmune licensed the monoclonal antibody, further developed it for human use, and conducted clinical trials showing that it could protect high-risk infants from severe RSV disease.

Impact

Following FDA approval in 1998, MedImmune marketed the RSV antibody Synagis® for prevention of severe RSV disease in high-risk infants. Monthly administration of Synagis during RSV season reduces RSV-related hospitalizations by an estimated 45 to 55 percent[20]. Because RSV is an important pediatric pathogen and an increasingly recognized cause of severe respiratory disease in chronically ill adults and the elderly, RSV vaccine research and development continues to be a high priority in the IRP.

Publications

Prince GA, Hemming VG, Horswood RL, Chanock RM. Immunoprophylaxis and immunotherapy of respiratory syncytial virus infection in the cotton rat. *Virus Res*. 1985 Oct;3(3):193-206.

Murphy BR, Sotnikov A, Paradiso PR, Hildreth SW, Jenson AB, Baggs RB, Lawrence L, Zubak JJ, Chanock RM, Beeler JA, et al. Immunization of cotton rats with the fusion (F) and large (G) glycoproteins of respiratory syncytial virus (RSV) protects against RSV challenge without potentiating RSV disease. *Vaccine*. 1989 Dec;7(6):533-40.

1985(+): Hitting HIV hard with HAART therapy

Challenge

The human immunodeficiency virus (HIV), discovered in 1984[21], is a retrovirus that causes progressive failure of the immune system, resulting in the development of opportunistic infections and cancers (acquired immunodeficiency syndrome, or AIDS). Development of therapies is imperative to stop viral replication and progression of the disease.

Advance

Soon after HIV was found to be the cause of AIDS, IRP researchers Samuel Broder, M.D., Hiroaki Mitsuya, M.D., Ph.D., and Robert Yarchoan, M.D., demonstrated that certain nucleoside reverse transcriptase inhibitors had activity against HIV in the test tube, a discovery the team rapidly moved to test in clinical trials.

Impact

This research yielded the first drugs approved by the U.S. FDA for the treatment of HIV infection: zidovudine (AZT) in 1985, didanosine (ddI) in 1991, and zalcitabine (ddC) in 1992. These drugs became the foundation for highly active antiretroviral therapies (HAART), saving countless lives.

Publications

Yarchoan R, Mitsuya H, Thomas RV, Pluda JM, Hartman NR, Perno CF, Marczyk KS, Allain JP, Johns DG, Broder S. In vivo activity against HIV and favorable toxicity profile of 2',3'-dideoxyinosine. *Science*. 1989 Jul 28;245(4916):412-5.

20 http://pediatrics.aappublications.org/content/112/6/1442.full.pdf
21 http://history.nih.gov/nihinownwords/docs/page_04.html

procedures

Procedures and Therapies

2012: Exposing "silent" heart attacks through novel imaging techniques

Challenge

Each year, about 1.2 million people in the U.S. have heart attacks[22], but not all heart attacks are visible with electrocardiography (EKG). Rapid and accurate methods to detect and manage "silent" heart attacks are needed to speed diagnosis and ensure timely treatment.

Advance

IRP scientists led by Andrew E. Arai, M.D., pioneered the use of non-invasive magnetic resonance imaging (MRI) to accurately detect and respond to unrecognized myocardial infarctions.

Impact

For the first time, physicians are able to detect, monitor, and treat heart attacks that patients may not even know had occurred. Early intervention in this type of cardiac damage can reduce the likelihood of subsequent cardiac events, including heart failure.

Publications

Schelbert EB, Cao JJ, Sigurdsson S, Aspelund T, Kellman P, Aletras AH, Dyke CK, Thorgeirsson G, Eiriksdottir G, Launer LJ, Gudnason V, Harris TB, Arai AE. Prevalence and Prognosis of Unrecognized Myocardial Infarction Determined by Cardiac Magnetic Resonance in Older Adults. *JAMA*. 2012;308(9):890-896.

22 http://www.nhlbi.nih.gov/health/health-topics/topics/heartattack/

2012: Open your eyes to the power of image-based online searching

Challenge

Illustrations in medical literature contribute greatly to understanding complex biomedical concepts—for researchers, scientists, and the lay public alike. However, bibliographic databases are mostly text-based; hence the need for systems that deliver citations enriched by visual material, for example, radiographic images, photographs, sketches, graphs or charts.

Advance

Dina Demner-Fushman, M.D., Ph.D., and Sameer Antani, Ph.D., led the development of Open-i (pronounced "open eye"), a novel open-access biomedical image search engine. In addition to image search capabilities, Open-i also provides outcome—or "take away"—statements extracted from a collection of 250,000 open access articles and 1 million illustrations in the biomedical literature hosted at the National Library of Medicine's PubMed Central® repository.

Impact

As the first production-quality system of its kind in the biomedical domain, Open-i enables medical professionals and the public to access both highly relevant visual information and key outcome statements from biomedical publications. Just a few months after public release, the site had more than 5,000 unique visitors per day and was ranked 382nd in the world (among 30 million Web sites)[23].

Publications

The Open-i Website: http://openi.nlm.nih.gov/index.php.

2011: Advancing rapid detection of prion diseases

Challenge

Prion diseases, such as Creutzfeldt-Jacob disease (CJD) in humans, scrapie in sheep, and mad cow disease in cattle, are difficult to diagnose, currently untreatable, and ultimately fatal. People and animals can be infected for years before symptoms appear. A faster and more practical prion diagnostic test that does not require cerebrospinal fluid sampling or brain tissue could simplify screening for prion diseases and allow earlier diagnostic confirmation to guide healthcare decision-making.

Advance

IRP scientists led by Byron Caughey, Ph.D., developed a prion blood test called enhanced Quaking-Induced Conversion (eQuIC), which uses an antibody to isolate abnormal prion protein from blood plasma and then amplifies it to enhance detection. The test is 10,000 times more sensitive for detecting variant CJD than previously described tests. The National Institute of Allergy and Infectious Diseases (NIAID) and its project partner, Swiss diagnostics firm Prionics AG, have applied for a patent on the eQuIC test.

Impact

eQuIC could be used by blood banks, hospitals, livestock operations, and rendering plants to screen for prion diseases in a far more efficient and less invasive manner than current diagnostic tools. Additionally, this concept of testing for abnormal proteins could eventually be applied to the diagnosis of other diseases, such as Alzheimer's, Huntington's, and Parkinson's disease, but more research is needed and underway.

23 http://www.webstatsdomain.com/domains/openi.nlm.nih.gov/

Publications

Orrú CD, Wilham JM, Raymond LD, Kuhn F, Schroeder B, Raeber AJ, Caughey B. Prion disease blood test using immunoprecipitation and improved quaking-induced conversion. *MBio*. 2011 May 10;2(3):e00078-11.

2011: Pioneering closed-chest hole-in-the-heart repair

Challenge

One of the most common congenital heart diseases is ventricular septal defect, or "hole-in-the-heart." Current repair techniques require open-chest surgery and prolonged exposure to ionizing radiation to visualize the appropriate anatomy. Non-surgical interventions would reduce risks and improve recovery times.

Advance

Robert J. Lederman, M.D., and colleagues tested a pre-clinical MRI-guided, catheter-based, closed-chest intervention that provides enhanced image guidance, reduced radiation exposure, and reduced surgical risk.

Impact

If clinical trials continue to support development of MRI-guided treatments, pediatric patients with ventricular septal defect could avoid the risks associated with traditional surgical interventions in favor of a less invasive and safer procedure.

Publications

Ratnayaka K, Saikus CE, Faranesh AZ, Bell JA, Barbash IM, Kocaturk O, Reyes CA, Sonmez M, Schenke WH, Wright VJ, Hansen MS, Slack MC, Lederman RJ. Closed-chest transthoracic magnetic resonance imaging-guided ventricular septal defect closure in swine. *JACC Cardiovasc Interv*. 2011 Dec;4(12):1326-34.

2011: Taking the random out of biopsy sampling

Challenge

Biopsy is currently the only way to confirm a diagnosis of prostate cancer. However, despite improvements in technology, prostate biopsy sampling remains a challenge, and cancerous lesions may be missed. Novel diagnostic tools are needed to ensure more accurate biopsies and better cancer detection rates.

Advance

Peter L. Choyke, M.D., Peter A. Pinto, M.D., Bradford Wood, M.D., and colleagues developed a combined magnetic resonance imaging (MRI) and ultrasound-guided prostate biopsy, a minimally invasive technique that allows for the detection of cancer at a far higher rate than current biopsy techniques.

Impact

Fusion MRI/ultrasound-guided biopsy has been shown in clinical trials to detect more instances of cancer than standard biopsies, consequently leading to more accurate diagnosis and more appropriate course of treatment for cancer patients.

Publications

Turkbey B, Xu S, Kruecker J, Locklin J, Pang Y, Shah V, Bernardo M, Baccala A, Rastinehad A, Benjamin C, Merino MJ, Wood BJ, Choyke PL, Pinto PA. Documenting the location of systematic transrectal ultrasound-guided prostate biopsies: correlation with multi-parametric MRI. *Cancer Imaging*. 2011 Mar 29;11:31-6.

2010: The Teaching Tool: A digital cervix for colposcopists

Challenge

Colposcopy—examination of the cervix with a specialized microscope—is a widely used diagnostic technique for cervical cancer, a disease that affects nearly a quarter of a million women in the U.S.[24]. There is an ongoing need for effective knowledge assessment in this area, both for medical professionals in training and working clinicians seeking to advance their skills. Since colposcopy is image-based, an image-based assessment allowing for interaction with the images would be ideal.

Advance

IRP researchers led by Rodney Long, M.A., in collaboration with colleagues at the American Society for Colposcopy and Cervical Pathology (ASCCP), have developed the Teaching Tool, an interactive online assessment system for medical professionals in the field of colposcopy. This system uses cervicography images to simulate views of the uterine cervix as seen through a colposcope, and includes two assessment exams given by the ASCCP: one for medical professionals in training, and the other for established clinicians.

Impact

Since its release in 2010, the Teaching Tool has been used nationwide in more than 100 Resident Programs in Ob/Gyn and Family Practice, and at institutions such as the Mayo Clinic, Georgetown University, Baylor College of Medicine, and Duke University Medical Center. The tool has been used to give more than 1,000 exams to physicians in training and over 200 established medical professionals who use colposcopy in their practices.

Publications

The Teaching Tool: http://infocus.nlm.nih.gov/2012/04/innovative-collaboration-produ.html.

2008(+): Diseases with no diagnosis: Providing relief for the rare and unknown

Challenge

For individuals with rare and unknown diseases, there is no greater goal than an accurate diagnosis leading to possibilities of therapeutic relief. Doctors and scientists have long recognized the path to diagnosis as an opportunity to learn more about human disease. A program aimed at providing answers and insight could help both patients and researchers.

Advance

The NIH Undiagnosed Diseases Program (UDP) was established in 2008 and has since seen more than 150 patients a year. The success of the program is illustrated best through the discovery and diagnosis of rare disorders, such as when William A. Gahl, M.D., Ph.D., and colleagues uncovered a rare arterial calcification disease. By conducting clinical, radiographic and genetic studies in three families, the researchers eventually identified a novel gene mutation that causes a protein deficiency.

Impact

The UDP has received thousands of applications since opening, with approximately 10 percent of the program's patients receiving a full diagnosis, and a further 30 percent gaining partial diagnosis. The researchers of the UDP continue to work tirelessly to discover the cause of those ailments still undiagnosed, along the way finding new biochemical, genetic and molecular pathways, and furthering our knowledge of human disease.

24 http://seer.cancer.gov/statfacts/html/cervix.html

Publications

NIH Launches Undiagnosed Diseases Program: http://www.genome.gov/27026388.

St Hilaire C, Ziegler SG, Markello TC, Brusco A, Groden C, Gill F, Carlson-Donohoe H, Lederman RJ, Chen MY, Yang D, Siegenthaler MP, Arduino C, Mancini C, Freudenthal B, Stanescu HC, Zdebik AA, Chaganti RK, Nussbaum RL, Kleta R, Gahl WA, Boehm M. NT5E mutations and arterial calcifications. *N Engl J Med.* 2011 Feb 3;364(5):432-42.

2006(+): Inventing sharper and faster optical microscopes for live cell imaging

Challenge

Microscopes have traditionally evolved in tandem with medical research, and scientists today need new generations of microscopes to enable them to delve even deeper into the molecular mechanisms of disease.

Advance

IRP investigators, including Clare M. Waterman, Ph.D., Jennifer Lippincott-Schwartz, Ph.D., and Hari Shroff, Ph.D., have pioneered new imaging techniques and tools, such as fluorescent speckle microscopy (FSM), photoactivation localization microscopy (PALM), and inverted selective plane illumination microscopy (iSPIM), that provide dramatically clearer views of healthy and diseased live cells, their organelles, and the protein interactions within.

Impact

Through improved imaging, researchers around the world can now visualize complex developmental and disease progressions that previously could only be conjectured. The ability to visualize cellular organelles and macromolecules in such fine detail provides researchers with new tools to accelerate understanding of cellular function in health and disease.

Publications

Kanchanawong P, Shtengel G, Pasapera AM, Ramko EB, Davidson MW, Hess HF, Waterman CM. Nanoscale architecture of integrin-based cell adhesions. *Nature*. 2010 Nov 25;468(7323):580-4.

Betzig E, Patterson GH, Sougrat R, Lindwasser OW, Olenych S, Bonifacino JS, Davidson MW, Lippincott-Schwartz J, Hess HF. Imaging intracellular fluorescent proteins at nanometer resolution. *Science*. 2006 Sep 15;313(5793):1642-5. Epub 2006 Aug 10.

Wu Y, Ghitani A, Christensen R, Santella A, Du Z, Rondeau G, Bao Z, Colón-Ramos D, Shroff H. Inverted selective plane illumination microscopy (iSPIM) enables coupled cell identity lineaging and neurodevelopmental imaging in Caenorhabditis elegans. *PNAS*. 2011 Oct 25;108(43):17708-13. doi: 10.1073/pnas.1108494108. Epub 2011 Oct 17.

1996: Dissecting good from bad with laser-capture microdissection

Challenge

Due to the mixture of cell types in a tumor biopsy, the ability to separate the different cells in order to study them discretely has been a long-standing problem in research.

Advance

IRP scientists led by Michael R. Emmert-Buck, M.D., Ph.D., William M. Bonner, Ph.D., and Lance Liotta, M.D., Ph.D., invented laser-capture microdissection (LCM) to rapidly and precisely select specific cells from a biopsy sample. Using a low-energy laser beam and special transfer film, LCM enables researchers to isolate normal, precancerous, and cancer cells for analysis.

Impact

This novel technology provides a solution to the problem of isolation and purification of distinct cells within a given tissue sample. LCM has become a well-established research tool used throughout the world, and has been enhanced and expanded into many new biomedical applications.

Publications

Emmert-Buck MR, Bonner RF, Smith PD, Chuaqui RF, Zhuang Z, Goldstein SR, Weiss RA, Liotta LA. Laser capture microdissection. *Science*. 1996 Nov 8;274(5289):998-1001.